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10/604,400	07/17/2003	Eric T. KOOL	12665.0024.NPUS01	1399

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EXAMINER

STRZELECKA, TERESA E

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1637

DATE MAILED: 10/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

18

Office Action Summary	Application No. 10/604,400	Applicant(s) KOOL, ERIC T.	
	Examiner Teresa E. Strzelecka	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 July 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-49 is/are pending in the application.
- 4a) Of the above claim(s) 16-39, 42 and 43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15, 40, 41 and 44-49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>7/31/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This office action is in response to an amendment filed July 31, 2006. Claims 1-49 were previously pending, with claims 16-39, 42 and 43 withdrawn from consideration. Applicant amended claims 2-4.
2. Applicant's amendments overcame the rejection of claims 2-4 under 35 U.S.C. 112, second paragraph. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" section below.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on July 31, 2006 was filed after the mailing date of the non-final office action on April 18, 2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

4. Applicant's arguments filed July 31, 2006 have been fully considered but they are not persuasive.

A) Regarding claim interpretation, Applicant argues the following:

a) The term "fluorophore compound" is described in the specification as a unimolecular entity. Applicant specifically cites paragraph [0032] which states that "the molecule containing the fluorophore and the quenching group can be any molecule" and that Fig. 2 and 3 show single molecules. However, these are not definitions of the term, in the sense that there is no statement in the specification of the following form: "The term "fluorophore compound means...", "the term "fluorophore compound is..." or "The term "fluorophore compound" refers to...". Therefore, the

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interpretation of the term as a unimolecular or multimolecular entity is the broadest reasonable interpretation in view of lack of its definition.

b) The term “leaving group” is described in paragraph [0035] in terms of its function. As most of the fluorescent dyes and quencher molecules possess ring structures, their electronic structures would facilitate nucleophilic attack on the bonds connecting them to their nucleic acid bases. Therefore, basically any fluorescent molecule inherently possesses this property.

c) The term “quenching” is described in the specification, for example, in paragraphs [0019] or [0031]. However, there is no definition of this term in the specification. Further, as the quenching effect depends on the distance between two compounds and solution conditions, as well as on the degree of spectral overlap between the dyes, the degree of quenching for the same dye will change, therefore, it is a functional, not a structural, limitation.

B) Regarding the rejection of claims 1-7, 9 and 11-15, Applicant argues that the reference of Sando et al. is Applicant’s own work. However, this statement is insufficient to overcome the rejection (see MPEP 706.02(b) and 2132.01):

706.02(b) Overcoming a 35 U.S.C. 102 Rejection Based on a Printed Publication or Patent

A rejection based on 35 U.S.C. 102(a) can be overcome by:

(A) Persuasively arguing that the claims are patentably distinguishable from the prior art;

(B) Amending the claims to patentably distinguish over the prior art;

(C) Filing an affidavit or declaration under 37 C.F.R. 1.131 showing prior invention, if the reference is not a U.S. patent or a U.S. patent application publication claiming the same patentable invention as defined in 37 C.F.R. 41.203(a). See MPEP § 715 for information on the requirements of 37 C.F.R. 1.131 affidavits. When the claims of the reference U.S. patent or U.S. patent application publication and the application are directed to the same invention or are obvious variants, an affidavit or declaration under 37 C.F.R. 1.131 is not appropriate to overcome the rejection.

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(D) Filing an affidavit or declaration under 37 C.F.R. 1.132 showing that the reference invention is not by "another." See MPEP § 715.01(a), 715.01(c), and 716.10;

(E) Perfecting a claim to priority under 35 U.S.C. 119 (a)-(d) as explained in reference to 35 U.S.C. 102(e) above;

(F) Perfecting priority under 35 U.S.C. 119(e) or 120 as explained in reference to 35 U.S.C. 102(e) above.

2132.01 Publications as 35 U.S.C. 102(a) Prior Art

APPLICANT CAN REBUT *PRIMA FACIE* CASE BY SHOWING REFERENCE'S DISCLOSURE WAS DERIVED FROM APPLICANT'S OWN WORK

Applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982) (discussed below). Therefore, where the applicant is one of the co-authors of a publication cited against his or her application, the publication may be removed as a reference by the filing of affidavits made out by the other authors establishing that the relevant portions of the publication originated with, or were obtained from, applicant. Such affidavits are called disclaiming affidavits. *Ex parte Hirschler*, 110 USPQ 384 (Bd. App. 1952). The rejection can also be overcome by submission of a specific declaration by the applicant establishing that the article is describing applicant's own work. *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). However, if there is evidence that the co-author has refused to disclaim inventorship and believes himself or herself to be an inventor, applicant's affidavit will not be enough to establish that applicant is the sole inventor and the rejection will stand. *Ex parte Kroger*, 219 USPQ 370 (Bd. Pat. App. & Int. 1982) (discussed below). It is also possible to overcome the rejection by adding the coauthors as inventors to the application if the requirements of 35 U.S.C. 116, third paragraph are met. *In re Searles*, 422 F.2d 431, 164 USPQ 623 (CCPA 1970).

In *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982), Katz stated in a declaration that the coauthors of the publication, Chiorazzi and Eshhar, "were students working under the direction and supervision of the inventor, Dr. David H. Katz." The court held that this declaration, in combination with the fact that the publication was a research paper, was enough to establish Katz as the sole inventor and that the work described in the publication was his own. In research papers, students involved only with assay and testing are normally listed as coauthors but are not considered co-inventors.

In *Ex parte Kroger*, 219 USPQ 370 (Bd. Pat. App. & Inter. 1982), Kroger, Knaster and others were listed as authors on an article on photovoltaic power generation. The article was used to reject the claims of an application listing Kroger and Rod as inventors. Kroger and Rod submitted affidavits declaring themselves to be the inventors. The affidavits also stated that Knaster merely carried out assignments and

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worked under the supervision and direction of Kroger. The Board stated that if this were the only evidence in the case, it would be established, under *In re Katz*, that Kroger and Rod were the only inventors. However, in this case, there was evidence that Knaster had refused to sign an affidavit disclaiming inventorship and Knaster had introduced evidence into the case in the form of a letter to the PTO in which he alleged that he was a co-inventor. The Board held that the evidence had not been fully developed enough to overcome the rejection. Note that the rejection had been made under 35 U.S.C. 102(f) but the Board treated the issue the same as if it had arisen under 35 U.S.C. 102(a). See also case law dealing with overcoming 102(e) rejections as presented in MPEP § 2136.05. Many of the issues are the same.

The rejection is maintained.

C) Regarding the rejection of claims 1-8, 10, 11 and 14 under 35 U.S.C. 102(b) as anticipated by Livak et al. Applicant argues that the quencher dye of Livak et al. does not leave the probe. However, the structure of the probe taught by Livak et al. is such that the quencher would leave the probe under nucleophilic attack.

The rejection is maintained.

D) Regarding the rejection of claims 1, 5-7, 9 and 12-14 under 35 U.S.C. 102(b) as anticipated by Xu et al., Applicant argues that Xu et al. do not teach or suggest a fluorescence quenching leaving group. However, as explained in the arguments to claim interpretation, any fluorescent compound inherently possess a property of enabling a nucleophilic attack on the bond which joins to it to a base, therefore since both the ROX and HEX are acceptor dyes, they do quench the fluorescence of the donor dye.

The rejection is maintained.

E) Regarding the rejection of claims 40, 41, 44, 46 and 46 under 35 U.S.C. 103(a) over Sano et al., Tyagi et al. and Stratagene Catalog, Applicant argues that Sano et al. is not prior art. This argument was addressed above.

The rejection is maintained.

F) Regarding the rejection of claims 48 and 49 under 35 U.S.C. 103(a) over Sando et al., Tyagi et al., Stratagene Catalog and Seitz et al., Applicant argues that Sano et al. is not prior art. This argument was addressed above.

The rejection is maintained.

Claim Interpretation

5. Applicant did not define the term “fluorophore compound”, therefore it is interpreted as either unimolecular or multimolecular entity.
6. Applicant did not define the term “fluorescence quenching leaving group”, therefore it is interpreted as any fluorescence quenching group.
7. Applicant did not define what it means for the fluorescence to be quenched. For example, in the case of a fluorescence donor-acceptor pair, the fluorescence intensity of the donor usually decreases in the presence of the fluorescence acceptor, therefore in this case the acceptor is considered as a fluorescence quencher.
8. Applicant did not define the terms “about 2 fold”, “about 100 fold” and “about 1000 fold”, therefore any value of the quenching is considered as anticipating these terms, since the degree of quenching depends on the proximity of the two dye molecules, solution conditions and the spectral overlap of the emission and absorption spectra of the two dyes.
9. The art rejections presented below are based on different interpretation of the meaning of the term “fluorescence quenching leaving group”, as explained above.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-7, 9 and 11-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Sando et al. (J. Am. Chem. Soc., vol. 124, pp. 2096-2097, February 2002; cited in the IDS).

Regarding claim 1, Sando et al. teach a 13 bp nucleic acid probe comprising fluorescein (= fluorophore) and dabsyl (= fluorescence quenching group) (Fig. 1; page 2096, fourth paragraph).

Regarding claims 2-4, Sando et al. teach the efficiency of quenching of about 100 fold, anticipating the limitations of at least about 2 fold, 100 fold or 1000 fold.

Regarding claims 5 and 6, Sando et al. teach the compound being a nucleic acid (Fig. 1; page 2096, fourth paragraph).

Regarding claim 7, Sando et al. teach single-stranded nucleic acid (Fig. 1).

Regarding claim 9, Sando et al. teach the quenching group attached to the 5' hydroxyl (page 2096, fourth paragraph).

Regarding claim 11, Sando et al. teach fluorophore located three nucleotides away from the quencher (page 2096, fourth paragraph).

Regarding claims 12 and 13, Sando et al. teach 7mer probes comprising a phosphorothioate group (= nucleophilic group) at their 3' termini (page 2096, fourth paragraph).

Regarding claim 14, Sando et al. teach fluorescein (page 2096, fourth and last paragraphs).

Regarding claim 15, Sando et al. teach dabsyl (page 2096, fourth and last paragraphs).

12. Claims 1-8, 10, 11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Livak et al. (PCR Meth. Appl., vol. 14, pp. 357-362, 1995; cited in the IDS).

Regarding claim 1, Livak et al. teach a nucleic acid probe comprising a fluorophore FAM and a quencher TAMRA (Fig. 1; page 357, second and third paragraphs; page 358, first and last paragraphs; page 360, fourth paragraph).

Regarding claims 2-4, Livak et al. teach quenching efficiency of at least 2-fold (Fig. 2).

Regarding claims 5 and 6, Livak et al. teach nucleic acid probes (Fig. 1; page 357, second and third paragraphs).

Regarding claims 7 and 8, Livak et al. teach both single-stranded and double-stranded nucleic acid probes (Fig. 1; page 357, last paragraph; page 358, first paragraph; Table 1; page 360, second paragraph).

Regarding claim 10, Livak et al. teach the quenching group attached to the internal nucleotides and to the 3'-end of the probe (Fig. 1; Fig. 2).

Regarding claim 11, Livak et al. teach the quenching group attached one nucleotide away from the fluorophore (Fig. 2, probe A1-2).

Regarding claim 14, Livak et al. teach fluorescein and TAMRA (page 357, last paragraph; page 358, first paragraph).

13. Claims 1, 5-7, 9 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Xu et al. (Nat. Biotechnol., vol. 19, pp. 148-152, February 2001).

Regarding claim 1, Xu et al. teach a fluorophore compound consisting of two nucleic acid probe pairs, where the 13 bp probe contains a FAM fluorophore and the 7 bp probe contains either a ROX acceptor (= quencher) or a HEX acceptor (= quencher) (fig. 3; page 150, paragraphs 2-5).

Regarding claims 5 and 6, Xu et al. teach nucleic acid probes (Fig. 3).

Regarding claim 7, Xu et al. teach single-stranded probes (Fig. 3).

Regarding claim 9, Xu et al. teach the quenchers attached to the 5' hydroxyl group (Fig. 3; page 151, sixth paragraph).

Regarding claims 12 and 13, Xu et al. teach the compound comprising a nucleophilic phosphorothioate group (Fig. 3; page 151, fifth paragraph).

Regarding claim 14, Xu et al. teach ROX (Fig. 3).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejections based on the Sando et al. reference

15. Claims 40, 41, 44, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sando et al. (J. Am. Chem. Soc., vol. 124, pp. 2096-2097, February 2002; cited in the IDS), Tyagi et al. (U.S. Patent No. 5,925,917) and Stratagene Catalog (page 39, 1988).

A) Regarding claim 40, Sando et al. teach a composition comprising:

a first nucleic acid probe which hybridizes to H-ras oncogene sequence, the first probe comprising a fluorophore and a quencher (page 2096, fourth paragraph; Fig. 1), and

a second nucleic acid probe comprising a nucleophilic group (page 2096, fourth paragraph; Fig. 1), where the binding of the first and second nucleic acids probes to the target causes displacement of the quenching group (page 2096, fourth and fifth paragraphs; Fig. 1).

Regarding claim 41, Sando et al. teach the quenching group attached to the 5' hydroxyl of the first probe and the nucleophilic group attached to the 3' end of the second probe (page 2096, fourth paragraph; Fig. 1).

Regarding claim 44, Sando et al. teach the quenching group attached two nucleotides away from the fluorophore (page 2096, fourth paragraph; Fig. 1).

Regarding claims 46 and 47, Sando et al. teach DNA probes (page 2096, fourth paragraph; Fig. 1).

B) Sando et al. do not teach kits comprising the probes.

C) Tyagi et al. teach kits comprising probes labeled with fluorophores and quenchers (Fig. 1-5; col.24, lines 41-65; claims 79-88).

D) Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the probes of Sando et al. into a kit format as suggested by Tyagi et al. since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and premixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

16. Claims 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sando et al. (J. Am. Chem. Soc., vol. 124, pp. 2096-2097, February 2002; cited in the IDS), Tyagi et al. (U.S.

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Patent No. 5,925,917) and Stratagene Catalog (page 39, 1988) as applied to claim 40 above, and further in view of Seitz et al. (Angew. Chem. Int. Ed., vol. 39, pp. 3249-3252, 2000).

A) Teachings of Sando et al., Tyagi et al. and Stratagene Catalog are presented above. They do not teach probes being RNA, 2'-O-methyl-RNA, phosphorothioate DNA, LNA or PNA.

B) Steitz teaches PNA probes labeled with fluorophore and quencher (Fig. 1; Scheme 1).

It would have been *prima facie* obvious to use PNA probes of Steitz in the kit of Sando et al., Tyagi et al. and Stratagene Catalog. The motivation to do so, provided by Steitz, would have been that PNAs bind with very high affinity and selectivity to complementary nucleic acids (page 3249, second paragraph).

17. No claims are allowed.

Conclusion

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
10/11/06